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Associations of Weight Change With Changes in Calf Muscle Characteristics and Functional Decline in Peripheral Artery Disease

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Background—Among people with lower extremity peripheral artery disease, obesity is associated with faster functional decline than normal weight. The association of weight loss with functional decline in peripheral artery disease is unknown.

Methods and Results—Adults with an ankle-brachial index <0.90 were identified from Chicago-area hospitals in 2002–2004. Weight and 6-minute walk distance were measured annually. Weight change categories were weight loss or gain (≥ 5 pounds/year at ≥ 1 visit) or stable (weight change <5 pounds at each visit). Participants reported whether weight loss was “intentional” or “unintentional.” Calf muscle area was measured with computed tomography every 2 years. Associations of weight change with changes in calf muscle area and 6-minute walk distance were analyzed using mixed-effects models and adjusted for age, body mass index, ankle-brachial index, physical activity, and other confounders. Among 389 participants, mean ankle-brachial index was 0.63 ± 0.16 , mean age was 74.5 ± 7.8 , and mean body mass index was 28.1 ± 5.1 kg/m². Over 3.23 ± 1.37 years, muscle area declined more in adults with intentional weight loss versus stable or gain (pair-wise comparisons, $P < 0.001$). Intentional weight loss was associated with less annual decline in 6-minute walk distance than weight gain (intentional loss, 3.7 m; stable, -14.0 m; gain, -28.5 m; unintentional loss, -20.8 m; pair-wise comparison intentional loss versus gain, $P = 0.003$).

Conclusions—Despite a greater loss of calf muscle area, adults with peripheral artery disease who intentionally lost ≥ 5 pounds experienced less functional decline than those who gained weight. A randomized trial is needed to establish whether benefits of weight loss in peripheral artery disease outweigh potential adverse effects. (*J Am Heart Assoc.* 2019;8:e010890. DOI: 10.1161/JAHA.118.010890.)

Key Words: obesity • observational studies • peripheral artery disease • physical exercise

Prevalence of overweight or obesity is increasingly common among adults with peripheral artery disease (PAD).^{1–4} Recent evidence demonstrated that $>65\%$ of adults with PAD are overweight or obese.^{3–5} Among adults with PAD,

a higher body mass index (BMI) at baseline is associated with more adverse changes in calf muscle characteristics over time, greater functional decline, and a poorer response to exercise training compared with normal weight adults with PAD.^{1,6–11} In addition, adults with PAD who are overweight or obese are more likely to require a lower extremity revascularization and experience a cardiovascular event than those with a normal BMI.^{7,12}

Whether weight loss or weight gain are also associated with changes in lower extremity characteristics or functional decline in PAD is not well understood. A previous study did not show a significant association between weight loss or gain with functional decline overall; however, adults who gained 5 to 10 pounds but exercised regularly had less functional decline than adults who did not gain weight but also did not exercise.¹³ An important consideration is whether or not weight loss is intentional. Unintentional weight loss is often marked by poor health status and frailty, thus potentially confounding any association between weight change and functional decline.¹⁴ For example, using data from the Cardiovascular Healthy Study, Ix et al found an inverse association between BMI and incident PAD in the whole

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Clinical Perspective

What Is New?

- Adults with peripheral artery disease with ≥ 5 pounds intentional weight loss experienced less annual decline in the 6-minute walk than adults who gained ≥ 5 pounds.
- The slower decline in 6-minute walk occurred despite a significantly greater reduction in muscle area among those who lost weight compared with those who gained weight.
- There was no difference between groups in knee extension strength or power.

What Are the Clinical Implications?

- Prevalence of overweight or obesity among adults with peripheral artery disease is as high as 75%, and yet clinical practice guidelines do not address treatment of overweight or obesity.
- Encouraging weight loss may help mitigate functional decline among adults with peripheral artery disease.
- However, a clinical trial is needed to demonstrate that the benefits outweigh potential harms.

cohort.¹ However, after excluding adults who reported poor health or unintentional weight loss, the researchers found a positive association between BMI and incident PAD.

Given the high prevalence of overweight and obesity among adults with PAD, it is important to understand the prognostic implications of changes in weight.^{1–4} Therefore, the purpose of these analyses was to delineate associations of changes in weight with changes in calf muscle characteristics and functional decline in PAD. We hypothesized that people with PAD who lost weight intentionally would experience a greater decline in muscle mass, but would experience less functional decline than adults with PAD with unintentional weight loss, or those whose weight remained stable or who gained weight.

Methods

The protocol for this study was approved by the institutional review boards at Northwestern University Feinberg School of Medicine (Chicago, IL) and by all participating centers. All participants gave written informed consent. Methods have been previously described.^{8,15} The data supporting the findings of this study are available from the corresponding author upon reasonable request, within constraints allowed by the institutional review board.

Patient Identification

The study cohort was identified from participants who completed baseline testing in the WALCS II (Walking and

Leg Circulation Study II) between May 2002 and May 2004.^{15–17} Participants were aged 59 years and older at baseline. An ankle-brachial index (ABI) < 0.90 was used as the criterion to define PAD.

Data were collected between May 6, 2002 and October 16, 2009. Participants completed a baseline visit and up to 4 annual follow-up visits. Calf muscle characteristics were measured by computed tomography (CT) at baseline and at 2- and 4-year follow-up assessments. Functional outcomes were measured at baseline and at each annual follow-up visit.

Exclusion Criteria

Exclusion criteria have been described previously and are summarized here.¹⁶ Participants with dementia, recent major surgery, or lower extremity amputations were excluded. Nursing home residents and wheelchair-bound participants were excluded. Non-English-speaking participants were excluded because investigators were not fluent in non-English languages.

Ankle-brachial Index

ABI was measured at the baseline visit, using established methods.^{18,19} Systolic blood pressures in the right and left brachial, dorsalis pedis, and posterior tibial arteries were obtained using a handheld Doppler probe (Vascular Pocket Dop II; Nicolet, Golden, Colo), and each pressure was measured twice.^{18,19} The ABI was calculated for each leg by dividing the mean of the dorsalis pedis and posterior tibial pressures by the mean of the 4 brachial pressures. When the brachial pressure in 1 arm was higher than in the opposite arm, and the 2 brachial pressures differed by 10 mm Hg, the arm with highest pressure was used in the denominator for ABI calculation because subclavian stenosis was potentially present in these instances.²⁰ The ABI for the leg with the lowest ABI was used in the statistical analyses for calf muscle characteristics.

Weight and Weight Change

Weight was measured at baseline and all annual follow-up visits. BMI was calculated as weight (kilograms) divided by height (meters) squared. All weight change refers to annual change. Weight loss was defined as ≥ 5 -pound decrease and weight gain was defined as ≥ 5 -pound increase compared with the previous year's visit, at 1 or more of the follow-up visits. Stable weight was defined as any weight change from the previous year that was < 5 pounds at all visits.

We chose a 5-pound cutoff for weight loss or gain because it could be clinically meaningful, but also more easily achievable without a formal weight-loss program. In addition

to measuring weight at each visit, participants were asked whether they experienced at least a 5-pound weight loss between visits. For those who responded that they had lost ≥ 5 pounds, their weight loss was categorized as “intentional” or “unintentional” based on their response to the following question: “Was the weight loss intentional, that is, were you trying to lose the weight?” The question was asked starting at follow-up visit 2, and so data about whether or not weight loss was intentional are not available at baseline and follow-up visit 1. Participants were only classified as having lost weight if their measured weight between study visits decreased by ≥ 5 pounds. Participants who reported weight loss but whose measured weight at follow-up visits did not decrease by ≥ 5 pounds were classified based on their measured weight.

Calf Muscle Characteristics

Calf muscle characteristics were measured at baseline and every 2 years using a CT scanner (LightSpeed; General Electric Medical Systems, Waukesha, WI) and BonAlyse software (BonAlyse OY, Jyväskylä, Finland).^{17,21} Cross-sectional CT images (2.5-mm) of the calves were obtained at 66.7% of the distance from the distal to the proximal tibia, the point of maximal muscle cross-sectional area.²² Scanned images were analyzed by BonAlyse software, which distinguishes between muscle tissue, fat, and bone by detecting different density thresholds, using the density of water as the reference. Bone and subcutaneous fat were excluded from analyses. Muscle area was quantified by summing voxels within the range corresponding to muscle density (9–271 mg/cm³). Intramuscular fat was quantified by summing voxels corresponding to fat tissue (–270 to 8 mg/cm³). This method of estimating muscle area has been validated through previous cadaveric studies and is shown to be highly correlated with direct anatomical measurements.²²

Leg Strength and Muscle Power

Isometric knee extension strength and knee extension power were measured at baseline and at each annual follow-up visit. Isometric knee extension strength was assessed using the Good Strength Chair (Metitur Oy, Jyväskylä, Finland).^{23,24} Participants were seated in the chair and instructed to push against secure leg attachments for 5 seconds. The leg attachments were fixed with strain gauges that were linked by transducers to a computer that recorded the measurements. From 2 trials, the highest value was used.

Knee extension power was assessed using a power rig.^{24,25} Participants were seated with their arms folded across the chest and asked to push a footplate that was connected to a flywheel. The final velocity of the flywheel was measured by an optoswitch attached to a microcomputer, from which

average power could be derived. Each push lasted between 0.20 and 0.40 seconds, and up to 10 consecutive trials were used to obtain maximum power.

Six-Minute Walk Test

In the 6-minute walk test, participants walked back and forth along a 100-foot hallway with instructions to cover as much distance as possible, based on previously described methods.^{26,27}

Comorbidities

Participant comorbidities were identified using algorithms from the Women’s Health and Aging Study and Cardiovascular Health Study, which combined data from patient report, physical examination, medical record review, medications, laboratory values, and a primary care physician questionnaire.²⁸ These criteria were used to document angina, cancer, diabetes mellitus, heart failure, myocardial infarction, pulmonary disease, stroke, spinal stenosis, and disk disease. American College of Rheumatology criteria were used to diagnose knee and hip arthritis.²⁹

Walking Exercise Activity

During each study visit, participants were asked, “During the past 2 weeks, have you gone walking for exercise?” Frequency and duration of walking for exercise were also determined at each visit. Based on earlier studies, a minimum frequency of 3 times per week and a minimum duration of 30 minutes per session are most optimal for supervised walking exercise programs in patients with PAD.³⁰ Therefore, participants were classified as exercising regularly if they walked ≥ 3 times for ≥ 30 minutes per session, per week.

During each study visit, participants were also asked how many blocks they had walked in the past week.

Other Measures

Occurrence of lower extremity revascularization and hip or knee replacement surgery during follow-up was obtained by patient report and ascertained by medical record review or a primary care physician questionnaire. Cigarette smoking was assessed by patient report. Medication use was assessed at each study visit. Participants brought their medication bottles or a list of medications to their study visit. The study principal investigator (M.M.M.) and study first author (T.S.P.) identified which participants were taking statin, antiplatelet medication (aspirin or clopidogrel), and cilostazol, blinded to participant characteristics. We used the Social Security Administration Death Index to search for deaths through May 23, 2009.

Information on deaths was also obtained from family members, proxies, and primary care physicians.

Statistical Analyses

Participants were included in the analyses if they returned for at least 1 follow-up visit. Over the course of the study, participants may have met criteria for more than 1 weight change category. However, when calculating baseline characteristics, participants were classified into mutually exclusive categories. Adults who met the criterion for weight loss at ≥ 1 follow-up visit, but also met the criterion for weight gain at other follow-up visits were classified as “fluctuate.” Participants who lost weight at ≥ 1 visit, and whose weight remained stable at other study visits, were classified as having lost weight. Participants who gained weight at ≥ 1 visit, and whose weight remained stable at other study visits, were classified as having gained weight. Baseline characteristics across weight change categories (weight loss, weight gain, stable, and fluctuate) were compared using general linear regression models for continuous variables and chi-square test for categorical variables. When analyzing baseline characteristics, participants with weight loss were not stratified by intentional versus unintentional, because the question was only included in the study protocol starting at the second follow-up visit. Agreement between reported and measured weight loss of ≥ 5 pounds was assessed using the kappa statistic.

To compare annual changes in 6-minute walk, calf muscle characteristics, knee extension strength, and knee extension power, the mixed-effects linear regression analysis was used with a subject-specific random intercept. This accounted for the possibility that each participant’s annual change in outcomes was correlated with their previous annual change. The weight change categories for annualized changes in lower extremity outcomes were intentional weight loss, unintentional weight loss, stable weight, and weight gain. The fluctuate category was excluded from the longitudinal analyses because the regression was based on weight changes between successive annual visits. For analyses involving intentional versus unintentional weight loss, the changes in outcomes from baseline to first annual follow-up were excluded, because participants were not asked whether their weight loss was intentional until the second follow-up visit.

Annual increments of weight change were analyzed (rather than longer-term changes) given the likelihood that the largest association with 6-minute walk and knee extension strength and power would likely occur in close proximity to the weight changes. Because CT scans were performed every 2 years, participants were classified based on the 2-year net change in weight for analyses related to calf muscle area and percent fat. For example, if a participant lost 6 pounds intentionally between the first and second follow-up visits, but gained 4

pounds between the second and third follow-up visits (net 2-year weight loss of 2 pounds), then the participant would be classified as having stable weight for the CT measures only. However, for the 6-minute walk and knee extension strength and power, which were measured annually, the participant would contribute 1 person-year each to the intentional weight loss and stable weight categories.

Person-years for each weight change category were summed from the successive annual changes at each follow-up visit. The number of person-years a participant contributed depended on how long they remained with the study. Some participants contributed person-years to more than 1 weight change category (eg, weight loss between baseline and the first follow-up visit, but weight stable between the first and second visits). Skipped interim visits were handled as missing data. Annual weight change was not calculated for skipped visits. Time between consecutive visits was not included as a covariate.

Dependent variables were the successive changes in 6-minute walk distance, calf skeletal muscle characteristics, leg strength, and power. Analyses were adjusted for age, race, sex, BMI, ABI, smoking, comorbidities, regular exercise, the number of blocks walked per week, medication use (aspirin or clopidogrel, statin, and cilostazol), tibia length (muscle area and knee extension measures only), lower extremity revascularization during follow-up, hip or knee replacement during follow-up, presence of arthritis, and previous year muscle measure (for muscle outcomes) or previous year functional performance (for functional outcomes) or previous leg strength and power measures (for leg strength and power outcomes). For the outcome of the 6-minute walk, we also evaluated results without adjustment for physical activity and medication use.

Results

Four hundred sixty-three participants with PAD completed baseline testing in the WALCS II cohort. Thirty-eight participants were excluded because they did not attend a follow-up visit. An additional 36 participants who attended a follow-up visit were excluded because of missing baseline information or outcome data. Ultimately, 389 participants who completed at least 1 follow-up visit were included in analyses. Mean follow-up was 3.23 ± 1.37 years.

Mean age was 74.8 ± 7.8 years, and mean ABI was 0.63 ± 0.16 . Table 1 shows participant characteristics according to weight change category. Mean BMI was in the overweight range in all groups, with prevalence of overweight or obesity ranging from 65% in the stable weight category to 81% in the fluctuate group. Compared with PAD participants with stable weight, those who lost ≥ 5 pounds during follow-up included a higher prevalence of men and a higher baseline

Table 1. Baseline Characteristics of Participants With Peripheral Artery Disease According to Weight Change Category During Follow Up (n=389)

Variable	Loss (n=136)	Stable (n=108)	Gain (n=67)	Fluctuate (n=78)	P Value
Age, y	75.5 (6.7)	75.0 (8.0)	72.6 (8.7)	73.5 (8.2)	0.04
Male, %	58.1	53.7	46.3	56.4	0.44
Black, %	16.9	15.7	19.4	15.4	0.91
Ankle-brachial index	0.63 (0.15)	0.63 (0.16)	0.61 (0.16)	0.65 (0.16)	0.63
Baseline BMI, kg/m ²	28.11 (4.80)	26.80 (4.54)	28.05 (5.62)	29.74 (5.37)	0.002
Overweight, %	43	43	46	36	0.61
Obese, %	31	22	28	45	0.01
Mean weight change during study, pounds (SD)					
Mean weight loss	10.25 (5.93)	n/a	n/a	12.46 (8.83)	0.02
Mean weight gain	n/a	n/a	9.76 (5.89)	9.58 (7.08)	0.85
Mean number of visits with weight change	1.22	n/a	1.12	2.55	0.001
Diabetes mellitus, %	30.88	29.63	40.30	34.62	0.47
Angina, %	33.33	37.14	40.30	29.87	0.55
Myocardial infarction, %	22.79	26.85	38.81	22.08	0.07
Stroke, %	19.85	26.85	19.40	15.38	0.27
Lower extremity arthritis, %	18.4	15.7	17.9	19.2	0.87
Pulmonary disease, %	44.85	39.81	41.79	44.87	0.96
Cancer, %	26.47	15.74	8.96	24.36	0.013
Calf muscle					
Area, mm ² , SD	5602 (1309)	5474 (1543)	5273 (1512)	5583 (1386)	0.46
Percentage of fat, %	9.55 (8.68)	9.87 (12.57)	14.48 (17.48)	12.13 (13.73)	0.047
Isometric knee extension strength, N	274.56 (108.60)	283.99 (113.66)	263.07 (103.06)	280.97 (119.15)	0.77
Knee extension power, W	96.02 (50.52)	93.85 (48.57)	88.02 (60.00)	104.65 (53.01)	0.32
Six-minute walk distance, meters	351.37 (105.49)	342.05 (118.06)	331.92 (146.26)	337.61 (129.88)	0.72

Values are expressed as mean (SD), unless otherwise indicated. Stable, weight change within 5 pounds in all visits; Loss, lost ≥ 5 pounds at least 1 visit and never gained ≥ 5 pounds; Gain, gained ≥ 5 pounds at least 1 visit and never lost 5 or more pounds; Fluctuate, both lost and gained ≥ 5 pounds throughout course of study. BMI indicates body mass index; n/a, not applicable.

prevalence of cancer. Participants who gained weight had a higher baseline prevalence of diabetes mellitus, angina, and myocardial infarction and black race. The number of participants who attended each follow-up visit are shown in Figure. Overall, 164 (42.2%) of the 389 participants attended all follow-up visits. There were no deaths between the baseline visit and the first follow-up visit; 63 participants (16.2%) died during follow-up.

Table 2 includes a comparison of baseline characteristics between those who were included in the analyses, those who were excluded because they did not attend any follow-up visits, and those who attended follow-up visits but were excluded because of missing baseline information or outcome data. Adults who were excluded were slightly older, were more likely to have pulmonary disease, and had a smaller calf area than those who were included. Mean BMI was >25 kg/m² in all 3 categories.

There was moderate correlation between self-report of weight loss ≥ 5 pounds and whether the participant actually lost ≥ 5 pounds based on measured weights at follow-up visits (kappa, 0.43; Table 3). Participants with PAD reported weight loss of ≥ 5 pounds over 233 person-years. Of these, there were 122 (52%) person-years in which participants had measured weight loss ≥ 5 pounds, consistent with their report. There were 180 person-years in which participants had a measured weight loss of ≥ 5 pounds at ≥ 1 follow-up visits. Over 122 of 180 (68%) person-years, participants responded “yes” to the question, “Since your most recent WALCS visit, have you lost 5 or more pounds of weight?” For the remaining 58/180 person-years, the participants had responded that they had not lost weight and so were classified as unintentional weight loss given that they did not recognize that they had lost weight.

The magnitude of weight change, stratified by annual weight change category and BMI, is shown in Table 4. Among

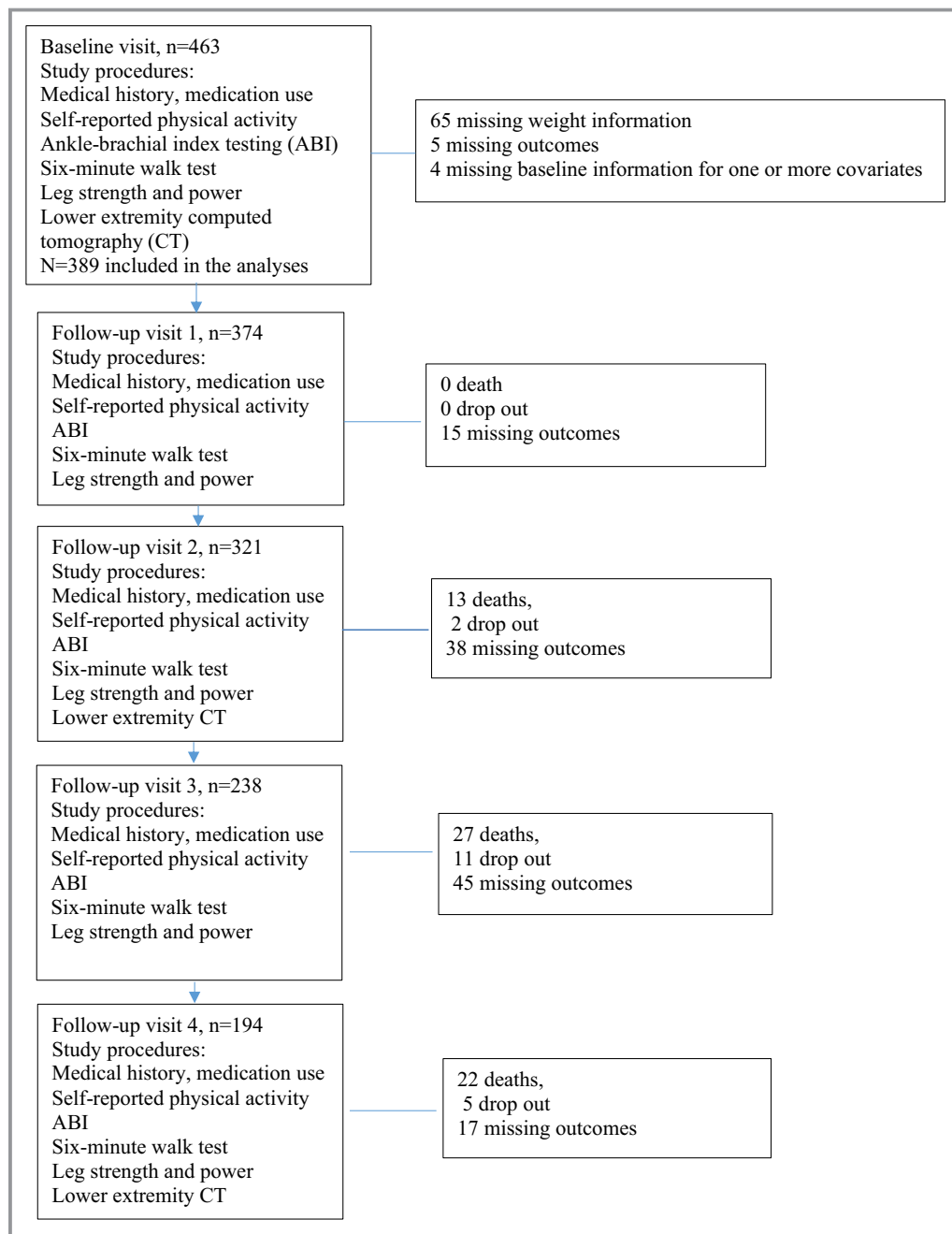


Figure. Study flow, walking, and leg circulation study.

participants who gained weight, the amount of annual weight gain was similar regardless of the previous year's BMI, and ranged from 8.8 to 10.7 pound. Adults who were obese and lost weight intentionally lost larger amounts of weight (17.5 ± 11.7 pounds) compared with obese participants with unintentional weight loss (12.9 ± 9.6 pounds). Degree of weight loss among overweight participants was similar between those with intentional (9.8 ± 4.0 pounds) and unintentional weight loss (9.9 ± 6.1 pounds).

Additional potential confounders of the association between weight change and lower extremity outcomes are

shown in Table 5. Use of statins, aspirin, clopidogrel, or cilostazol was similar in the 4 weight change categories. Regular walking exercise was uncommon among participants in all weight change categories. However, adults with intentional weight loss walked more blocks in the past week than other categories.

In multivariable analyses, PAD participants with intentional weight loss had the smallest decline in the 6-minute walk (model 3, intentional loss $+3.7$ m; weight stable, -14.0 m; weight gain, -28.5 m; unintentional loss, -20.8 m; Table 6). In the fully adjusted pair-wise comparisons, there was a

Table 2. Comparison of Baseline Characteristics Among Participants Who Were Included and Excluded From the Analyses

Variable	Included (N=389)	Excluded: Did Not Attend Any Follow-up Visits (N=38)	Excluded: Attended Follow-up Visits but Had Missing Data (N=36)	P Value
Age, y (SD)	74.5 (7.8)	78.2 (10.3)	77.3 (9.9)	0.006
Male, %	54.5	50.0	44.4	0.47
Black, %	16.7	13.2	25.0	0.36
Ankle-brachial index, (SD)	0.63 (0.16)	0.63 (0.15)	0.62 (0.18)	0.96
Baseline BMI, kg/m ² (SD)	28.1 (5.1)	25.9 (4.1)	27.6 (6.0)	0.059
Overweight, %	42.2	42.9	25.0	0.16
Obese, %	30.8	14.3	37.5	0.078
Diabetes mellitus, %	32.9	29.0	30.6	0.86
Angina, %	34.9	46.0	28.6	0.28
Myocardial infarction, %	26.5	31.6	19.4	0.49
Stroke, %	20.8	29.0	22.2	0.51
Lower extremity arthritis, %	15.9	7.9	13.9	0.41
Pulmonary disease, %	42.9	47.4	50.0	0.012
Cancer, %	20.1	18.4	19.4	0.97
Calf muscle				
Area, mm ² (SD)	5505.5 (1428.3)	5102.2 (996.2)	4757.5 (1624.9)	0.005
Percentage of fat, % (SD)	11.0 (12.8)	8.4 (7.1)	16.2 (15.2)	0.030
Isometric knee extension strength, N, (SD)	276.8 (111.1)	252.1 (102.3)	256.8 (121.0)	0.45
Knee extension power, W, (SD)	95.8 (52.2)	70.1 (36.0)	90.9 (66.8)	0.032
Six-minute walk distance, meters, (SD)	342.8 (121.3)	310.9 (124.8)	306.1 (107.9)	0.13

BMI indicates body mass index.

significant difference in the annual change in 6-minute walk between intentional versus unintentional weight loss ($P=0.022$) and intentional weight loss versus weight gain ($P=0.003$), but not those with intentional weight loss versus stable weight ($P=0.067$).

In pair-wise comparisons, adults with intentional weight loss had a significantly greater decrease in muscle area than

adults who gained weight and whose weight was stable ($P<0.001$ for both). There was no significant difference in the change in calf muscle area between those with intentional versus unintentional weight loss. In pair-wise comparisons, the increase in percent fat, and the change in knee extension strength and power among adults with intentional weight loss, was not significantly different from the other groups.

Associations of clinical characteristics with annual change in 6-minute walk are shown in Table 7. Adults with unintentional weight loss were excluded, given that the association between unintentional weight loss and change in 6-minute walk was so different from that of intentional weight loss. In a multivariable regression analysis, age, male sex, current smoking, and a higher baseline BMI were significantly associated with decline in the 6-minute walk. With regard to weight change, for every pound gained there was an additional decline in the 6-minute walk distance by 0.96 m.

Table 3. Associations of Actual vs Self-Reported Weight Loss Among People With Peripheral Artery Disease (n=720 visits)

	Self-Reported Weight Loss		
	Yes	No	Total Person-Years
Actual weight loss			
Yes (total %)	122 (16.9)	58 (8.1)	180
Row %	68	32	
Column %	52	12	
No	111 (15.4)	429 (59.6)	540
Row %	21	79	
Column %	48	88	
Total person-years	233	487	720

Discussion

In this longitudinal, observational cohort of 389 adults with PAD, almost three-quarters (71%) of the participants were

Table 4. Mean Weight Change Between Annual Follow-up Visits, Stratified by Weight Change Category and BMI (N=1003 visits)*

Previous Year BMI	Weight Change Among Those With Intentional Weight Loss	Weight Change Among Those With Unintentional Weight Loss	Weight Change Among Those With Stable Weight	Weight Change Among Those With Weight Gain
BMI 18 to <25, pounds of weight loss (SD)	−14.3 (−)	−7.7 (1.9)	−0.2 (2.6)	10.7 (7.8)
	1 person-year	37 person-years	192 person-years	38 person-years
BMI 25 to <30, pounds of weight loss (SD)	−9.8 (4.0)	−9.9 (6.1)	−0.1 (2.7)	8.8 (3.9)
	18 person-years	52 person-years	278 person-years	61 person-years
BMI ≥30, pounds of weight loss (SD)	−17.5 (11.7)	−12.9 (9.6)	−0.1 (2.8)	9.8 (7.7)
	24 person-years	48 person-years	180 person-years	74 person-years

BMI indicates body mass index.

*Person-years with missing data regarding intentional/unintentional weight loss were excluded.

overweight or obese. The high prevalence of overweight or obesity in the current study is similar to the prevalence in population-based cohorts, and suggests that an important component of treatment for PAD should address obesity.^{2–4} We found that adults with PAD who intentionally lost weight had significantly less decline in 6-minute walk performance, compared with participants with PAD who gained weight or who had unintentional weight loss. The substantially smaller decline in 6-minute walk distance among people with intentional weight loss occurred despite greater declines in calf muscle area compared with participants who maintained stable weight or who gained weight. The pair-wise comparisons between intentional weight loss and weight gain and unintentional weight loss remained statistically significant and were even stronger after adjusting for physical activity. A key finding of this study is that, with regard to changes in weight, the change in 6-minute walk is not consistent with changes in muscle characteristics. These results also highlight that adults with unintentional weight loss represent a vulnerable population, given that the magnitude of decline in the 6-minute walk was similar to that of adults who gained weight.

To our knowledge, no previous studies have assessed associations between changes in body weight, lower extremity

muscle characteristics, and function among people with PAD. However, several randomized, controlled trials of weight loss in obese older adults without PAD have shown favorable effects on functional performance. For example, in a randomized trial of 93 obese adults aged ≥65 years, those randomized to calorie restriction lost -9.0 ± 5.4 kg and experienced a significantly greater improvement in multiple measures of physical function, including peak oxygen consumption, gait speed, and balance, compared with the control group, despite a decrease in muscle mass.³¹ In the third arm of the trial, which combined exercise and diet, exercise attenuated, but did not completely mitigate, muscle and bone loss observed with weight loss. An analysis of 3 weight-loss trials that incorporated calorie restriction with physical activity showed that every 1-kg loss of fat mass predicted a 0.01-m/s increase in walking speed, independent of loss of lean mass.³² In another weight-loss trial, Villareal et al demonstrated that older adults randomized to resistance plus aerobic exercise experienced less decline in muscle mass than those randomized to aerobic or resistance training alone.³³

There are several potential explanations for why intentional weight loss could mitigate functional decline observed in PAD, despite a decrease in muscle area. Weight loss may simply

Table 5. Annual Medication Use and Annual Self-Reported Measures of Physical Activity Among Adults With Peripheral Artery Disease

	Intentional Weight Loss	Weight Stable	Weight Gain	Unintentional Weight Loss
Statin use, n (%)	29 (61.7)	408 (63.6)	93 (53.1)	99 (67.8)
	47 person-years	642 person-years	175 person-years	146 person-years
Aspirin or clopidogrel use, n (%)	36 (76.6)	417 (65.0)	115 (65.7)	95 (65.1)
	47 person-years	642 person-years	175 person-years	146 person-years
Cilostazol use, n (%)	4 (8.5)	63 (10.1)	19 (11.2)	14 (9.6)
	47 person-years	622 person-years	170 person-years	146 person-years
Walking ≥30 min for ≥3 days a week, n (%)	12 (25.5)	121 (18.8)	24 (13.6)	25 (17.0)
	47 person-years	644 person-years	177 person-years	147 person-years
Mean number of blocks walked per week, (95% CI)	32.3 (18.5, 46.1)	28.3 (24.2, 32.3)	23.7 (17.1, 30.3)	21.5 (13.4, 29.6)
	47 person-years	622 person-years	170 person-years	146 person-years

Table 6. Associations of Weight Change Categories and Annual Change in Muscle and Functional Outcomes Among People With Peripheral Artery Disease, After Additional Adjustment for Physical Activity and Medication Use

					Pair-wise Comparisons Reference Intentional Weight Loss		
Outcomes	Loss (intentional)	Stable	Gain	Loss (unintentional)	P Value Unintentional	P Value Stable	P Value Gain
Calf muscle [‡]							
Area, mm ²	−521.3 (−665.3, −377.4) 34 person-years	−236.6 (−293.6, −179.7) 206 person-years	−92.9 (−187.6, 1.7) 77 person-years	−461.7 (−536.6, −386.8) 125 person-years	0.47	<0.001	<0.001
Percentage of fat, %	1.76 (0.53, 2.99) 34 person-years	1.58 (1.10, 2.06) 206 person-years	1.39 (0.58, 2.20) 77 person-years	0.87 (0.24, 1.51) 125 person-years	0.21	0.80	0.62
Isometric knee extension strength (Nm) [‡]	−24.0 (−44.9, −3.1) 19 person-years	−7.9 (−12.6, −3.1) 305 person-years	−6.6 (−17.4, 4.2) 72 person-years	−14.0 (−25.4, −2.5) 60 person-years	0.41	0.14	0.15
Knee extension power (W) [‡]	−3.0 (−10.5, 4.5) 31 person-years	1.1 (−0.7, 2.9) 452 person-years	1.8 (−2.2, 5.8) 118 person-years	−5.7 (−10.1, −1.3) 84 person-years	0.54	0.30	0.28
Six-minute walk distance (m)							
Model 1*	+3.0 (−15.2, 21.1) 44 person-years	−13.5 (−17.8, −9.2) 619 person-years	−27.1 (−36.2, −18.0) 164 person-years	−19.3 (−29.7, −8.8) 129 person-years	0.038	0.088	0.005
Model 2 [†]	+3.8 (−14.5, 22.1) 43 person-years	−13.5 (−17.8, −9.1) 616 person-years	−26.9 (−36.1, −17.7) 162 person-years	−19.5 (−30.0, −9.0) 129 person-years	0.031	0.075	0.004
Model 3 [‡]	+3.7 (−14.4, 21.9) 43 person-years	−14.0 (−18.3, −9.6) 594 person-years	−28.5 (−37.8, −19.1) 155 person-years	−20.8 (−31.2, −10.3) 128 person-years	0.022	0.067	0.003

*Model 1 includes adjustment for age, race, sex, body mass index, ankle-brachial index, smoking, comorbidities, tibia length (muscle area and knee extension measures only), lower extremity revascularization during follow-up, hip or knee replacement during follow-up, presence of arthritis, and previous year muscle measure (for muscle outcomes) or previous year 6-minute walk (for 6-minute walk) or previous leg strength and power measures (for leg strength and power outcomes).

[†]Model 2 includes model 1 plus the number of blocks walked in the past week, and whether participants engaged in regular walking exercise (defined as walking ≥3 times a week for ≥30 min per time).

[‡]Model 3 includes model 2 plus use of statins, aspirin, clopidogrel, or clostazol.

Table 7. Associations of Clinical Variables With Annual Change in 6-Minute Walk Among Adults With Peripheral Artery Disease*

Variable	Annual Change in 6-Minute Walk (m) (95% CI)	P Value
One-year change in weight (per 1-pound increase)	−0.96 (−1.58, −0.35)	0.002
Previous year's 6-minute walk (m)	−0.11 (−0.15, −0.07)	<0.0001
Age (per y increase)	−1.13 (−1.62, −0.65)	<0.0001
Male (yes vs no)	10.76 (3.05, 18.47)	0.006
Black (yes vs no)	−2.59 (−11.98, 6.81)	0.59
Smoking (yes vs no)	−12.25 (−23.00, −1.50)	0.026
ABI (per 0.1 unit increase)	11.81 (−10.87, 34.49)	0.31
Baseline body mass index (per 1 unit higher)	−1.41 (−2.24, −0.58)	0.001
Number of blocks walked per week	0.01 (−0.05, 0.07)	0.73
Cancer (yes vs no)	−0.41 (−8.96, 8.14)	0.92
Diabetes mellitus (yes vs no)	−1.68 (−9.62, 6.27)	0.68
Pulmonary disease (yes vs no)	−5.25 (−12.27, 1.77)	0.14
Previous myocardial infarction, angina, heart failure, or stroke (yes vs no)	−1.27 (−4.38, 1.83)	0.42
Arthritis (yes vs no)	−0.07 (−4.58, 4.44)	0.98
Previous lower extremity revascularization (yes vs no)	11.36 (−3.83, 26.55)	0.14
Lower extremity revascularization during follow-up (yes vs no)	10.46 (−3.56, 24.48)	0.14

*Adults with unintentional weight loss were excluded. ABI indicates ankle-brachial index.

improve exercise capacity because of the reduction in work required for physical activity.³⁴ However, in a study of treadmill testing in 46 adults with PAD, total exercise time and oxygen consumption were similar in the obese and nonobese participants.⁹ And yet, based on serial ABI testing, adults with obesity experienced a slower recovery after exercise than nonobese adults, suggesting that obesity has a direct effect on muscle perfusion. Mouse models have shown impaired nitric-oxide-dependent vasodilation and enhanced vasoconstriction in the hind limb of obese versus nonobese mice.³⁵ Inflammation contributes to exercise limitation in PAD and may be further exacerbated by obesity.^{35–40} Mouse models of obesity demonstrate an expansion of fat between and around skeletal muscle fibers, with an accumulation of proinflammatory macrophages and T cells.³⁶ Adipose tissue is also a source of inflammatory cytokines, such as interleukin (IL)-6 and tumor necrosis factor (TNF)- α , that have direct adverse effects on muscle; TNF- α impairs muscle protein synthesis and increases muscle protein degradation whereas IL-6 increases muscle protein degradation.⁴¹ It has also been demonstrated that TNF- α impairs endothelial function with a decreased blood and nutrient supply to skeletal muscle, thus reducing exercise endurance.³⁹ Finally, obesity may worsen functional decline in PAD through pathways involving mitochondrial function. A high-fat diet has been shown to downregulate genes responsible for mitochondrial biogenesis and function.⁴² Visceral fat promotes insulin resistance, which

then promotes muscle catabolism, impaired protein synthesis, and mitochondrial dysfunction.³³

It is also important to consider that other studies suggest that measurement of isotope-labeled creatine more accurately reflects muscle mass than estimates based on muscle area by CT.⁴³ In addition, previous studies have shown only a moderate correlation between muscle area and function, which may explain why we observed a decrease in muscle area, but an improvement in the 6-minute walk distance.⁴⁴

Our study has limitations. First, the proportion of participants who intentionally lost weight was small, and so we only evaluated modest amounts of weight loss. The results may have differed with larger changes in weight or with a larger proportion of adults who lost weight intentionally. It is possible that we lacked power to detect significant differences in knee strength or power and percent of fat in the calf muscle in the pair-wise comparisons. Second, there was only moderate correlation between actual weight loss and self-report of weight loss. It is possible that participants had lost weight, but then already regained it by their study visit. It is also possible that some of the participants lost weight because of treatment with diuretics, rather than a decrease in adiposity. Third, we did not objectively measure physical activity on all participants. However, the pair-wise comparisons for 6-minute walk were strengthened after adjustment for self-reported physical activity. Furthermore, previous randomized, controlled trials of exercise programs in older

adults have shown that exercise alone does not lead to substantial weight loss.^{31,45} Fourth, the cohort included PAD participants aged 59 years and older. Further study is needed to determine whether the results are generalizable to younger people with PAD. Fifth, only 42% of participants attended all 4 exams. However, our focus on annualized changes in lower extremity outcomes with changes in weight, rather than long-term changes, should have minimized the effect on our results.

Conclusion

Among adults with PAD, intentional weight loss was associated with less functional decline than adults who gained weight, despite adverse changes in muscle area. Although walking exercise remains the foundation of treatment for PAD, adults who are overweight or obese do not respond to walking exercise as well as adults who are normal weight. Given the high prevalence of overweight and obesity in PAD, future study with a randomized trial is needed to establish definitively the effects of weight loss in addition to exercise on lower extremity outcomes in PAD.

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